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Abstract: Background: Extracts of Hypericum perforatum have demonstrated in randomized trials (RCTs) to be effective in mild to moderate depressive episodes, However, as their use in daily practice may differ from that in RCTs we have conducted a study to achieve a better estimate of the range and frequency of adverse drug reactions (ADR) and the efficacy. Patients and Methods: In an observational study in Germany, adult outpatients with depressive syndrome were treated with an extract of St. John's Wort. Study duration was 12 weeks, with control visits every 4 weeks, Besides anamnestic data, the variables assessed were: evolution of ICD-l0 derived sympscore, Global Clinical Impression scale (GCI), and toleraoility, Results: 1,778 patients from 304 centers participated in the study (mean duration of disorder 7.3 ± 18.9 months), and 1,541 patients completed it. At the last control visit the ICD-l0 sum score had dropped by 63.1 % and the proportion of patients described as 'normal to mildly ill' (GCI-s) had increased from 21 .6% at admission to 72.4%. Regarding the GCI-i, 77% of the patients had improved 'very much' or 'much' at the last visit. This was consistent with their self-assessment (76%). Lower age and shorter duration of the disorder were associated with significantly better outcomes, The incidence of ADRs was 3,54% and had been decreasing continuously fram the first contra I visit onwards; serious ADRs did not occure, Conclusions: The herbai drug was weil tolerated, and no new or serious ADR were identified. In view of the limitations inherent to the study design, it can be concluded that extracts of St. John's Wort are effective as an antidepressant in the management of depression in daily practice.

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A Hypericum Extract in the Treatment of Depressive Symptoms in Outpatients: An Open Study

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Key Words
Hypericum perforatum · Herbal drugs · Phytotherapy · Antidepressant · Open-label trial · Phase 4 · Drug toxicity

Summary
Background: Extracts of Hypericum perforatum have demonstrated in randomized trials (RCTs) to be effective in mild to moderate depressive episodes. However, as their use in daily practice may differ from that in RCTs we have conducted a study to achieve a better estimate of the range and frequency of adverse drug reactions (ADR) and the efficacy. **Patients and Methods:** In an observational study in Germany, adult outpatients with depressive syndrome were treated with an extract of St. John's Wort. Study duration was 12 weeks, with control visits every 4 weeks. Besides anamnestic data, the variables assessed were: evolution of ICD-10 derived symptom score, Global Clinical Impression scale (GCI), and tolerability. **Results:** 1,778 patients from 304 centers participated in the study (mean duration of disorder 7.3 ± 18.9 months), and 1,541 patients completed it. At the last control visit the ICD-10 sum score had dropped by 63.1% and the proportion of patients described as 'normal to mildly ill' (GCI-s) had increased from 21.6% at admission to 72.4%. Regarding the GCI-i, 77% of the patients had improved 'very much' or 'much' at the last visit. This was consistent with their self-assessment (76%). Lower age and shorter duration of the disorder were associated with significantly better outcomes. The incidence of ADRs was 3.54% and had been decreasing continuously from the first control visit onwards; serious ADRs did not occure. **Conclusions:** The herbal drug was well tolerated, and no new or serious ADR were identified. In view of the limitations inherent to the study design, it can be concluded that extracts of St. John's Wort are effective as an antidepressant in the management of depression in daily practice.

Schlüsselwörter
Hypericum perforatum · Pflanzliche Medikamente · Phytotherapie · Antidepressivum · Offene Studie · Phase 4 · Medikamentenverträglichkeit

Zusammenfassung
Hintergrund: In randomisierten Studien (RCT) zeigen sich Johanniskrautextrakte in der Behandlung von Patienten mit milden bis mäßigen depressiven Episoden als wirksam. Da sich die Anwendung in der ärztlichen Alltagspraxis jedoch von RCTs unterscheiden kann, führten wir eine Studie durch, um Spektrum und Häufigkeit unerwünschter Arzneimittelwirkungen (UAW) sowie Aspekte der Wirksamkeit besser abschätzen zu können. **Patienten und Methode:** In einer offenen Studie in Deutschland wurden erwachsene Patienten, die an einem depressiven Syndrom litten, 12 Wochen lang (mit 4-wöchentlichen Kontrolluntersuchungen) ambulant mit einem Johanniskrautextrakt behandelt. Neben den anamnestischen Daten wurden folgende Variablen untersucht: ICD-10-basierter Symptomscore, Global Clinical Impression Scale (GCI), Verträglichkeit. **Ergebnis:** 1778 Patienten aus 304 Arztpraxen nahmen an der Studie teil (durchschnittliche Krankheitsdauer 7,3 ± 18,9 Monate) und 1541 beendeten die Studie. Bei der letzten Kontrolluntersuchung war der ICD-10-Summenscore um 63,1% gesunken. Der Anteil der Patienten, die sich als «normal bis leicht krank» (GCI-s) einstuften, war von 21,6% zu Beginn auf 72,4% am Ende der Studie gestiegen. Bezogen auf die GCI-i ging es 77% Patienten am Ende «sehr viel» oder «viel» besser, was mit der Selbsteinschätzung der Patienten (76%) gut übereinstimmte. Ein niedrigeres Alter und eine kürzere Erkrankungsdauer waren mit einem signifikant besseren Outcome verbunden. Die Inzidenz von UAW betrug 3,54% und nahm von der ersten Kontrolluntersuchung an kontinuierlich ab; schwerwiegende UAWs wurden nicht beobachtet. **Schlussfolgerung:** Das pflanzliche Medikament wurde gut vertragen; es wurden keine neuen oder schwerwiegenden UAW berichtet. Vor dem Hintergrund der Einschränkungen durch das Studiendesign kann die Intervention als wirksam in der Behandlung von Patienten mit Depressionen in der Alltagspraxis angesehen werden.

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Background

Depression is associated with significant social and functional impairments as well as high direct and indirect health care costs [1, 2]. Depressive disorders have been reported to cause even greater functional disability than diabetes, chronic lung disease, hypertension, or back pain [3]. Depressive disorder is a chronic disorder which is often characterized by relapses and recurrences. The lifetime risk of depression is 10–25% for women and 5–12% for men [4, 5]. Furthermore, epidemiological data suggest that 75–80% of patients experience recurrent depression. The rate and timing of recurrence mainly seems to depend on the type of recovery. In patients who recovered completely the rate of recurrence was much lower and the time to recurrence was much longer than in patients with residual symptoms [6].

Recent research in a setting comparable to daily practice has demonstrated that about 50% of patients respond to the first antidepressive monotherapy but only about 30% achieve remission [7]. The rate of remission can be increased to almost 50% when a second drug is used if the initial antidepressant drug fails. With an ongoing sequential monotherapy, with a change to a third or fourth drug, remission can be improved by an additional 10% each time [5]. However, in placebo-controlled trials high relapse rates of 40–60% were observed within 6 months after discontinuation of the antidepressant treatment [8, 9]. Therefore, further treatment strategies and more effective or better tolerated agents continue to be required in order to improve treatment outcomes in all 3 phases of depression management commonly accepted: (1) acute phase, usually 6–12 weeks; (2) continuation phase, in which the goal of the treatment is to maintain the absence of depressive symptoms for an additional 4–9 months so that the depressive episode can be considered completely resolved; and (3) maintenance phase, i.e. often several years during which the goal of the treatment is to prevent the recurrence of another distinct depressive episode.

The goal of treatment is to achieve full remission of symptoms, which may take up to 4 months, and to maintain remission. To this end, according to current guidelines the antidepressant to be given should be matched to the individual patient's requirements considering [10, 11]:

- previous treatment response to a particular drug,
- tolerability and adverse effects of a previously given drug,
- profile of side effects (e.g. sedation, weight gain),
- low lethality, if history or likelihood of overdose,
- concurrent physical illness or condition that may make the antidepressant more noxious or less tolerated,
- concurrent medication that may interact with the antidepressant drug,
- associated psychiatric disorder that may specifically respond to a particular class of antidepressant (e.g. obsessive compulsive disorder and serotonin reuptake inhibitors),
- patients' preference.

The study presented here is an open, descriptive, observational (case series) study with a proprietary ethanolic extract of Hypericum perforatum, conducted under conditions of daily practice in Germany. The scope of such studies is to obtain information on prescription modalities, acceptability, compliance of the medication, achieve a better estimate of the frequency of adverse effects (and possibly identify rare, hitherto unknown adverse reactions) and get a broader picture of the efficacy (e.g. inclusion of subgroups not studied in earlier trials) [12].

Patients and Methods

Study Design and Variables

Patients with depressive disorders were treated with a herbal preparation of Hypericum perforatum (Helarium®, Bionorica AG, Neumarkt, Germany) in a community-based outpatient setting in Germany. The physicians participating in this observational multicenter study included general practitioners, internists, neurologists, and psychiatrists. The diagnoses were descriptive in the wordings of the investigators (treating physician) and later coded according to ICD-10 (one main term and one descriptor term by R.B.). The ICD-derived scales were validated with the $HAMD_{17}$ and its subscores and correlated well (data presented elsewhere). Treatment was documented for adult outpatients with depressive symptoms that required a pharmacological intervention.

Patients with any contraindication for Hypericum, with poor tolerability in a previous treatment with Hypericum, or who currently participated in a clinical study were not included in the study. Hypericum dosage was initiated according to the recommendations in the package insert, but could subsequently be adjusted according to the physician's estimate regarding best balance of efficacy and tolerability. The length of the trial was set at 3 months in order to allow sufficient time for a response to consolidate and for clinical benefits to be evident.

Data assessment was performed at 4 times: at baseline and at weeks 4, 8, and 12 (study termination), with the idea of identifying adverse drug reactions (ADRs) and estimating change of symptoms in terms of early response and at study end to see the maximum achieved effect. Demographics (age, sex, marital and professional status) and psychiatric history (duration of current episode, current diagnosis, concomitant diseases and medication, prescribed dosage of Hypericum [Helarium® capsules or tablets]) were recorded at the baseline visit (table 1).

The Clinical Global Impression scale (CGI) was used to evaluate the extent of change during treatment with Hypericum, as the CGI can be widely used in psychiatry [13]. Severity was assessed by the 7-point CGI – severity scale (CGI-s; 1 = normal/not at all ill; 7 = extremely ill). The description of this scale states that 'the severity of illness item requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis'.

The extent of improvement was assessed by the 7-point CGI – improvement scale (CGI-i; 1 = very much improved; 7 = very much worse) at the 2nd, 3rd, and final visit. The CGI-i asks the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state. A patient's illness is compared to change over time and rated. Additionally, the patients also evaluated their status themselves by employing simplified versions of the CGI-s and the CGI-i.

ICD-10 criteria were used to construct a severity rating on a scale from 0 = absent, to 4 = severe; that is: (1) 'depression' (mood (affective) disorders, F30–F39): such as lowering of mood, loss of interest, lack of energy, reduction of self-esteem; (2) 'anxiety' (neurotic, stress-related, and somatoform disorders, F40–F44, F48): such as excess of

Table 1. Patient data at baseline and patient flow

Patients included, n	1778
Sex, n (%)	
– Male	367 (20.9%)
– Female	1411 (79.1%)
Age, years	
– Mean (SD)	49.76 (15.2)
– Range	18–97
Mean (SD) time suffering from disorder, months	7.3 ± 18.9
Profession, n (%)	1741 (97.9%)
– Housewife/man	440 (24.7%)
– Part-time	221 (12.4%)
– Full-time	611 (34.4%)
– Retired	314 (17.7%)
– Unemployed	155 (8.7%)
Marital status, n (%)	1741 (97.9%)
– Single	252 (14.2%)
– Married	1021 (57.4%)
– Widowed	246 (13.8%)
– Divorced	222 (12.5%)
Dropouts, n	237
– Due to patients request/withdrawal of consent	74
– Termination of treatment before 3rd visit	70
– Due to inefficacy	53
– Reason unknown	37
– Due to adverse effects (n)	3
Patients analyzed, n	1541
Concomitant treatments, n (%)	194 (10.91%)
– Antidepressive: tricyclic antidepressants	21 (1.18%)
– SSRI	17 (0.96%)
– MAO inhibitors	2 (0.11%)
– Hypericum	0 (0%)
– NaSSA	5 (0.28%)
– Antipsychotic: neuroleptics	15 (0.84%)
– Lithium	1 (0.06%)
– Anxiolytic: herbal	31 (1.74%)
– Hypnotic/sedative: benzodiazep./ Imidazopyridine	46 (2.59%)
– Hormonal: HRT	10 (0.56%)
– Cardiac: nitrates	0 (0%)
– Beta-blockers	3 (0.17%)
– Analgesic: NSAID	14 (0.79%)
– Varia, not psychopharmaceutical	27 (1.52%)
– Not pharmaceutical	2 (0.11%)

HRT: Hormonal replacement therapy; MAO inhibitor: Monoamine oxidase A inhibitor; NaSSA: Noradrenergic and specific serotonergic antidepressant; NSAID: Non steroidal anti-inflammatory drug; SSRI: Selective serotonin reuptake inhibitor.

anxiety and fears; (3) somatic symptoms related to anxiety/depression (neurotic, stress-related, and somatoform disorders, F40–F44, F48): such as cardiovascular, or digestive, or respiratory, or muscular troubles; (4) somatoform disorders (F45): such as multiple somatic troubles, refuses medical diagnoses, continuous suffering due to symptoms.

For each block, the sum score and the highest individual score were calculated. Furthermore, the patients were administered a visual analogue scale (VAS; ranging from 'I feel very bad' to 'I feel very well') with lower values indicating better subjective feelings. In addition, current treatments, modifications in the dosage of the herbal drug, as well as ADRs (mentioned spontaneously or after general question, respectively), were documented at all visits.

St. John's Wort (Hypericum perforatum)

One of the problems encountered with herbal extracts, even from St. John's wort, is the variation of their compounds between different preparations [15]. The herbal drug itself (i.e. the raw material) is a complex multicompound [16], and – depending on the extraction method – its extracts may differ in quantity and qualitiy [17]. However, Hypericum extraxts possess a moderate to high potency to inhibit the reuptake of monoamines, serotonin, dopamine, noradrenaline, and the amino-acid neurotransmitters GABA and glutamate. Unlike standard reuptake inhibitors, Hypericum exerts this reuptake inhibition in a non-competitive way by enhancing intracellular Na^+-ion concentrations [19]. Recent studies indicate that St. John's wort is capable of increasing the in-vivo dopamine release [19], appears to increase extracellular dopamine levels in the brain [20] and increase plasma concentration of dihydroxyphenylacetic acid (DOPAC), the main metabolite of dopamine, possibly by an inhibitory effect on dopamine beta-hydroxylase [21].

For this study, the extract provided by the manufacturer, was Helarium Hypericum®, a hypericum extract with 255–285 mg dry ethanolic extract per coated tablet, standardized to hypericin 0.3% and of a hyperforin content of 2–3%, or Helarium-425® with 425 mg dry ethanolic extract per capsule (DER 3.5–6:1). Helarium-425® is standardized to hypericin 0.1–0.3% and has a hyperforin content of max. 6%, flavonoid/rutoside min. 6% in the extract.

Statistical Methods

Statistical analysis was performed with WinSTAT 2001.1 for Windows (SPSS-validated). The continuous data are presented as means and standard deviations (SD); additionally, medians, 95% confidence intervals (CIs) as well as ranges, and numbers (n) of patients were calculated. Categorical data are presented using counts (n) and percentages rounded to 1 decimal place. All p values are 2-tailed, and $p < 0.05$ was considered statistically significant. Unless stated otherwise, values before versus after treatment were compared by means of the Student's t-test, or the χ^2-test for nominal or ordinal data. The safety population, defined as subjects who received ≥1 dose of any study drug and for whom post-dose data were available, were used in the analysis and evaluation of the safety variables.

The influence of demographic factors (age, duration of disorder, gender) and the ICD-10 derived score at admission and at the final visit were examined by multiple stepwise regression analyses.

Results

Demographics and Data at Admission

304 centers participated in this study with a total of 1,778 patients (1–17 patients per center), recruited during winter and spring 1999. The (cumulative) number of dropouts was 38 at visit 1 (after 28.1 ± 30.2 days), 115 at visit 2 (after 57.6 ± 32.7 days), and 237 patients at visit 3 (after 89.8 ± 36.6 days; table 1). Questioned about it, 810 patients (45.6%) reported having

Table 2. CGI-s at admission, at each control visit and LOCF (LOCF vs. admission, $p < 0.001$)

CGI	Visit 0	Visit 1	Visit 2	Visit 3	Last visit LOCF
Normal (not at all ill)	14 (0,8%)	28 (1,6%)	92 (5,2%)	275 (15,4%)	296 (16,6%)
Borderline mentally ill	88 (4,9%)	98 (5,5%)	156 (8,7%)	191 (10,7%)	214 (12%)
Mildly ill	282 (15,8%)	405 (22,7%)	649 (36,4%)	690 (38,7%)	769 (43,1%)
Moderately ill	607 (34%)	650 (36,4%)	525 (29,4%)	257 (14,4%)	310 (17,4%)
Markedly ill	616 (34,5%)	475 (26,6%)	191 (10,7%)	86 (4,8%)	130 (7,3%)
Severely ill	133 (7,5%)	63 (3,5%)	24 (1,3%)	15 (0,8%)	25 (1,4%)
Extremely ill	6 (0,3%)	4 (0,2%)	1 (0,1%)	0 (0%)	0 (0%)
N = 1784	1757 (98,5%)	1740 (97,5%)	1652 (92,6%)	1527 (85,6%)	1757 (98,5%)
Not assessable	11 (0,6%)	17 (1%)	14 (0,8%)	13 (0,7%)	13 (0,7%)
No data	21 (1,2%)	38 (2,1%)	126 (7,1%)	251 (14,1%)	21 (1,2%)

Table 3. Patients' self-assessment at control visits and rating according to CGI-i (LOCF vs. admission, $p < 0.001$)

Parameter	Visit 1	Visit 2	Visit 3	Last visit LOCF
Very much improved	61 (3.4%)	199 (11.2%)	518 (29.1%)	556 (31.3%)
Much improved	350 (19.7%)	745 (41.9%)	722 (40.6%)	795 (44.7%)
Minimally improved	856 (48.1%)	581 (32.7%)	218 (12.3%)	272 (15.3%)
No change	424 (23.8%)	103 (5.8%)	57 (3.2%)	87 (4.9%)
Minimally worse	33 (1.9%)	15 (0.8%)	9 (0.5%)	12 (0.7%)
Much worse	13 (0.7%)	13 (0.7%)	8 (0.4%)	14 (0.8%)
Very much worse	4 (0.2%)	3 (0.2%)	1 (0.1%)	5 (0.3%)
N = 1778	1741 (97.9%)	1659 (93.3%)	1533 (86.2%)	1741 (97.9%)
No data	37 (2.1%)	119 (6.7%)	245 (13.8%)	37 (2.1%)

had similar problems before; in 1,073 patients (60.3%) an organic cause had been excluded, whereas in 88 patients (4.9%) it was confirmed; 1,068 patients (60.1%) reported psychosocial stress preceding their problems, and 850 (47.8%) felt they were related to external events or circumstances. 64 patients (3.6%) admitted an addiction in the past, and 51 patients (2.9%) at the time of admission. The addictions reported ranged from alcohol (n = 72, 4%), pharmaceuticals (n = 17, 1%), drugs (n = 5, 0.3%) to those 'not specified' (n = 11, 0.6%).

The vast majority of the patients were diagnosed with depressive episodes (F32.0–F33.9; n = 1,481; 83.3%); other diagnoses could be classified as neurotic, stress-related and somatoform disorders, i.e. anxiety (F40–F48: n = 137; 7.71%), psychovegetative syndrome (F45.3: n = 123; 6.9%), exhaustion (F43–F43.9: n = 107; 6.0%), etc. Only 2 patients (0.1%) were diagnosed with bipolar disorder (F31.9). Considering the highest ICD-derived subscore, depression predominated in 892 patients (50.17%), while anxiety predominated in 735 (41.34%) and somatic symptoms of anxiety/depression in 151 patients (8.49%).

The treatments prescribed were either Helarium® tablets (n = 452; 25.42%) or Helarium-425® capsules (n = 1,319; 74.18%; no data: n = 7; 0.39%). The mean daily dose was 822.5 ± 205.4 mg dry ethanolic Hypericum extract at admission (range 425–1,700 mg) and 754.4 ± 231.1 mg at the last visit. The most commonly prescribed dosage schedules were an intake twice or three times daily (58.6% or 27.1% of the patients, respectively). These continued to be the favored schedules as the trial went on.

In addition to the Hypericum treatment, 492 patients (27.7%) received supportive psychotherapy (n = 335; 18.8%), specific psychotherapy (n = 56; 3.1%), gymnastics (n = 35; 2%), etc.

At admission, 145 (8.16%) of the patients discontinued their psychotropic medication, mostly antidepressants, anxiolytics, and hypnotics/sedatives. During the study, 134 patients received 194 new prescriptions, predominantly hypnotics/sedatives, antidepressants, and anxiolytics. Noteworthy is the low proportion of patients medicated at admission, and the very limited number of co-prescriptions which might reflect the mostly mild to moderate nature of the depressive disorders treated.

Outcomes

Clinical Global Impression

The proportion of patients described as 'normal' to 'mildly ill' increased from 21.6% at admission to 72.4% at the last visit (visit 3, last observation carried forward – LOCF, table 2). Consistently, the proportion of those rated as 'moderately ill' or 'worse' decreased from 76.6% to 26.5%. Regarding the CGI-i, at the last visit (LOCF) 77% of the patients were reported to have (very) much improved. That was consistent with the patients' self-assessments according to which 76%

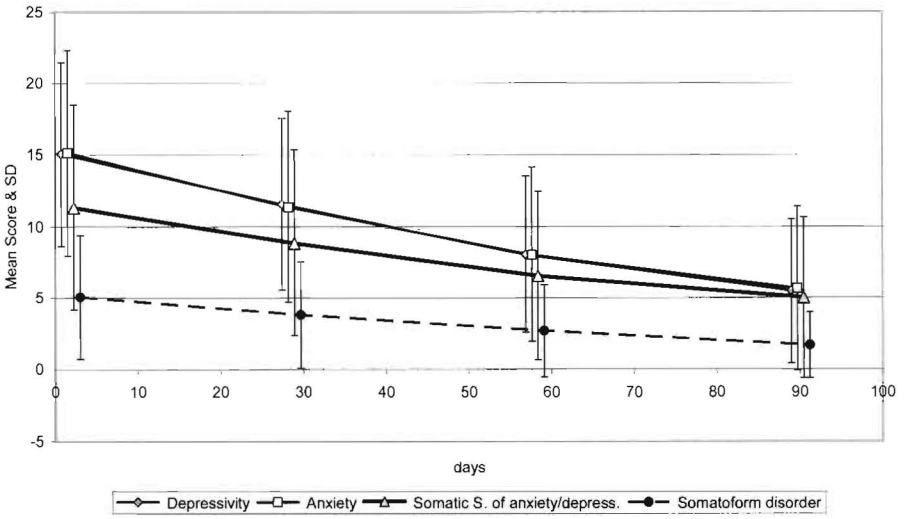

Fig. 1. Mean ICD-10 derived subscores for depression, anxiety, and somatic symptoms (10 items each; scores 0–40) and somatoform disorders (5 items; scores 0–20).

had improved (very) much (table 3). In all of these scales the improvement was progressive and largest at the end of the trial. Comparing the ratings at the last visit (LOCF) with those at admission, improvements were highly significant in all three of these variables.

ICD-10 Derived Scores

The ICD-10 derived scores are regarded as mean values of the 4 subscores over time and as mean scores of the individual symptoms at admission and at the last visit (patients 'on treatment'; fig. 1).

After 4 weeks of treatment (visit 1), the mean total sum score had diminished significantly by 23.6%, without major differences between subscores (depression: –23.2%, anxiety: –24.9%, somatic symptoms of anxiety/depression: –21.8%, somatoform disorder: –24.8%; all $p < 0.001$). The reduction had continued significantly at the 2nd control visit after approximately 8 weeks of treatment; the total sum score had diminished by 46% compared to admission (depression: –46.6%, anxiety: –47%, somatic symptoms of anxiety/depression: –42.2%, somatoform disorder: –47%; all $p < 0.001$). At the last control visit, the mean total sum score had dropped significantly by 63.1% with some differences between subscores, i.e. the somatic symptoms related to anxiety/depression diminished less, i.e. by 55.7% (depression: –63.6%, anxiety: –62.6%, somatoform disorder: –66.9%; all $p < 0.001$) (fig. 2).

Comparing the mean ICD-10 derived scores at admission and at visit 3 there is a homogeneous reduction of the individual symptoms rated. Noteworthy is the low score of suicidal thoughts already at admission, which seems indicative of the mostly mild to moderate nature of the depressive disorders treated.

Visual Analogue Scale (VAS)

The patients were administered a VAS at each visit. The steady and significant drop of its mean value indicates an improved subjective well-being of the patients. The difference was highly significant, i.e. $p < 0.001$, but there were no data of 33.4% of the patients.

Factors Affecting Outcome

Higher age, longer duration of the disorder (frequently associated with earlier episodes) and the ICD-10 derived sum score at admission were associated in stepwise regression analyses with a higher, i.e. worse, ICD-10 derived sum score at the final visit (constant: –5.95, ± 95% CI 3.98, $p = 0.003$; age: coefficient 0.08, ± 95% CI 0.05, $p < 0.001$; duration: coefficient 0.08, ± 95% CI 0.05, $p = 0.001$; ICD sum score at admission: coefficient 0.27, ± 95% CI 0.08, $p < 0.001$). Higher doses at admission were also associated with poorer outcomes ($p = 0.037$), probably reflecting more serious conditions at the outset. Comparing the improvements of the highest and lowest quintiles of the study sample by ICD-10 derived sum scores at admission, age or duration of disorder (variable: CGI-i at last visit LOCF), the ICD-10 derived sum score had no influence on the outcome. Lower age and shorter duration of disorder were associated significantly more often with being rated as 'very much improved'.

Safety

Patients rated the tolerance as 'very good' (n = 1,172; 65.92%), 'good' (n = 500; 28.12%) and 'moderate, poor or very poor' (n = 27; 1.51%; assessed: n = 1,721; 96.79%). The frequency of ADR was 3.54% (any event counted once per patient; table 4) and decreased from 2.9% at the first control visit to 1.2% at visit 2, and 1% at visit 3. The only ADR reported by >1% of the patients were gastrointestinal troubles and tiredness; followed by photosensibilization and restlessness (0.7% each).

In terms of adverse events, 5 patients (0.3%) were hospitalized due to psychiatric reasons and 1 due to an aggravation of a previously known colitis ulcerosa before the first control

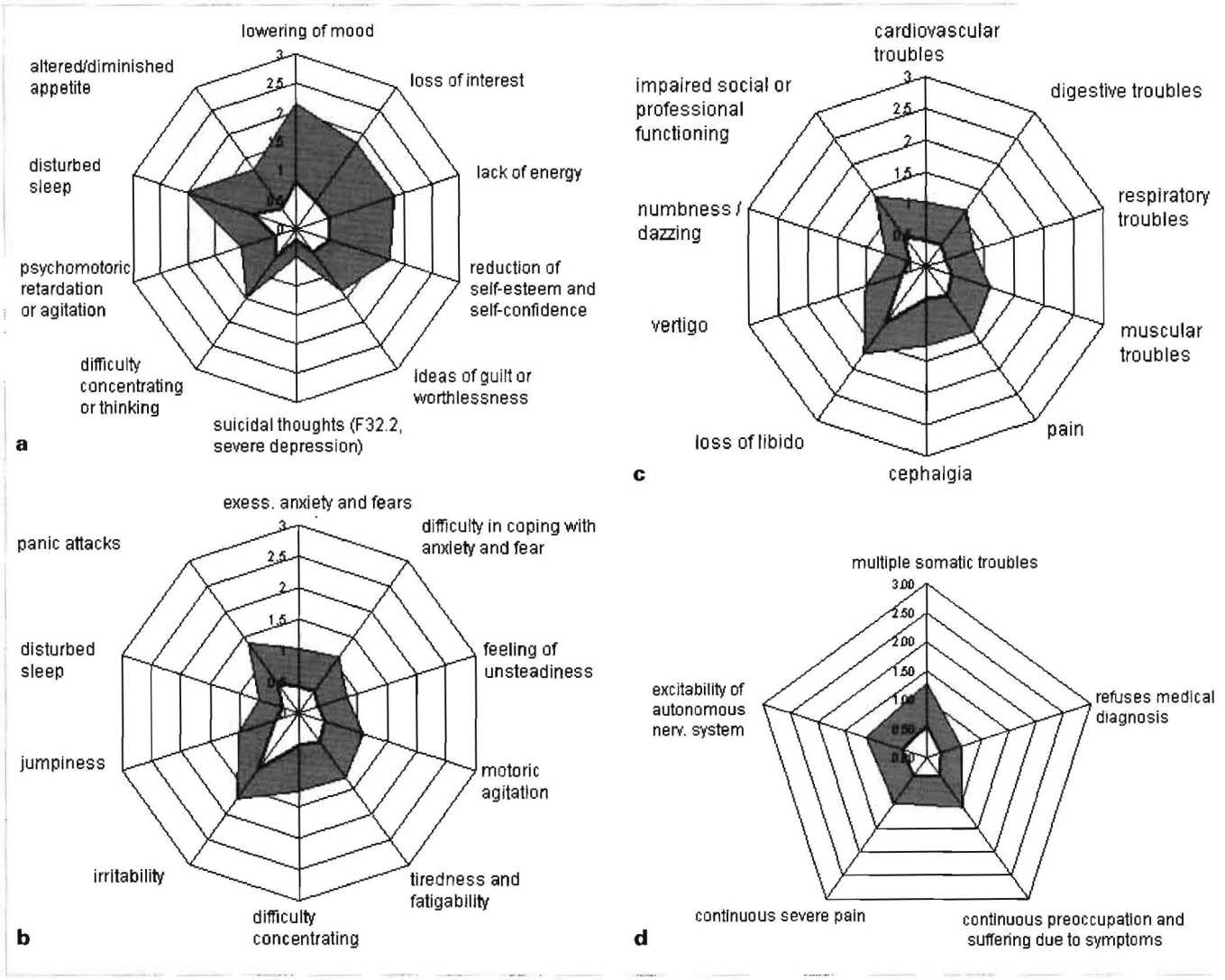

Fig. 2. Mean ICD-10 derived symptom scores for rating of the severity of **a** depression, **b** anxiety, **c** somatic symptoms related to depression or anxiety, **d** somatoform disorders related to depression or anxiety (■ = admission and □ = visit 3, scores 0–4).

Table 4. Summary of ADRs recorded at each visit and total

ADR	Visit 1	Visit 2	Visit 3	Total
Gastrointestinal troubles	16 (0.9%)	5 (0.28%)	4 (0.22%)	20 (1.12%)
Tiredness	12 (0.67%)	8 (0.45%)	7 (0.39%)	19 (1.07%)
Photosensibilization	11 (0.62%)	3 (0.17%)	2 (0.11%)	11 (0.62%)
Restlessness	9 (0.51%)	2 (0.11%)	3 (0.17%)	10 (0.56%)
Allergic skin reaction	2 (0.11%)	2 (0.11%)	1 (0.06%)	3 (0.17%)
Appetite increased	2 (0.11%)	0 (0%)	0 (0%)	2 (0.11%)
Dizziness, headache	1 (0.06%)	1 (0.06%)	1 (0.06%)	1 (0.06%)
Constipated	1 (0.06%)	0 (0%)	0 (0%)	1 (0.06%)
Polyuria	1 (0.06%)	0 (0%)	0 (0%)	1 (0.06%)
Acroparesthesias	1 (0.06%)	0 (0%)	0 (0%)	1 (0.06%)
Difficulty swallowing capsule	1 (0.06%)	0 (0%)	0 (0%)	1 (0.06%)
Vertigo	0 (0%)	1 (0.06%)	0 (0%)	1 (0.06%)
ADRs, n	57	22	18	71
Patients with ADRs, n	52 (2.92%)	21 (1.18%)	17 (0.96%)	63 (3.54%)

visit. There were no deaths reported in this study. A housewife aged 57 taking Helarium 425® was reported to have severely increased photosensitivity during the first month of treatment and was withdrawn from the trial. She received no other medication at the time and no other data of interest were reported. Another female, aged 67 years, also withdrew

from the trial due to increased photosensitivity and a male patient, aged 63 years, withdrew due to a 'side effect' not specified further.

The frequency of ADRs was similar in patients who received comedication, whether psychotropic or not. However, the number of these patients is relatively small (n = 134). Cutaneous reactions, including increased photosensitivity, were reported more frequently in males (due to more exposure to sunlight?) whereas digestive troubles and tiredness were more frequent among female patients.

Discussion

The latest metaanalysis of RCTs found Hypericum preparations to be superior to placebo in patients with major depression, to be similarly effective and to have fewer side effects than standard antidepressants [22]. Yet, a trend for decreasing effect sizes over time in trials of St. John's wort was seen in another metaanalysis [23], suggesting that St. John's wort may be less effective in treating depression than previously thought. More recent trials – which include only patients with documented major depression or large proportions of patients who have suffered from their current depressive episode for >2 years – may have excluded groups that are particularly responsive to Hypericum extract [24]. Consistent with this observation, the strengths of the study presented here is that it found a poorer outcome in patients with longer duration of the disorder, higher age and – less consistently – a higher symptom score at admission. This increases our knowledge of the factors that affect the treatment response. These finding were also observed in a large cohort of outpatients treated with selective serotonin reuptake inhibitors (SSRI) [25]. Furthermore, considering the highest ICD-derived subscore, depression prevailed in half of the cases, anxiety prevailed in 41.3% of the cases and somatic symptoms of anxiety/depression were highest in 8.5% of the patients. This stratification had no relevant influence on the outcomes. However, these results somehow correspond with data on the comorbidity of depression and anxiety as well as with associations between somatic complaints and depression and they could give an additional rational for the use of Hypericum [26, 27]. While it would be premature to draw any conclusions concerning efficacy from these observational findings, they may be of interest to generate hypotheses for future trials with Hypericum, because a consistent and progressive reduction of these symptoms could be seen in the ICD-10 derived scores (anxiety, somatoform, and somatic symptoms). Yet, one has to be aware that placebo effects, the natural course of the disorder, and regression to the mean can result in high rates of good outcomes that may be misattributed to the specific treatment [28, 29].

Possible shortcomings of this study are that most of the patients investigated had only mild to moderate depression, thus the results cannot be extrapolated to patients with more severe depression. Yet, the patient group studied here corresponds to a community-based population generally found in outpatient settings. Furthermore, although we found that the duration of depression correlated negatively with the duration of the disorder, this could not be analyzed in more detail due to a lack of data. Finally, the ICD-10 score used may seem unusual. Yet it was chosen in order to facilitate a transfer of the physicians' diagnoses in daily practice into diagnostic categories. In order to ensure correspondence with commonly used psychometric instruments, the ICD-derived scales were validated with the $HAMD_{17}$ and its subscores and correlated significantly.

Although St. John's wort is generally well tolerated in clinical trials, increasing attention has been given to its tendency to compromise the effectivity of other medications (e.g., cyclosporine, HIV protease inhibitors, oral contraceptives, digoxin, warfarin, and theophylline) by interactions mediated through cytochrome P450 enzymes [30] and transport protein P-glycoproteins [31]. Thus, prescribers should beware of possible decreases in the systemic bioavailability of conventional drugs [32] especially with Hypericum extracts rich in hyperforin [33, 34]. In the study presented here, comprising a total of 1,778 patients, the frequency of adverse effects was low (3.54% of the patients), decreased over time and was similar in patients who received comedication, whether psychotropic or not. There were neither serious nor unexpected ADRs. This low incidence of ADRs with Helarium® is in line with formerly published data on Hypericum preparations, especially Hypericum preparations not enriched in hyperforin [35].

Conclusions

In this open observational study, the herbal preparation of Hypericum perforatum was well tolerated and no new or serious adverse effects were identified. In view of the limitations of the study design, it may be concluded that Hypericum perforatum was a quite effective antidepressant for mild to moderate depression. A positive treatment response was favored by a more recent onset of the disorder, lower age of the patients and, possibly, less severe symptoms at baseline.

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Conflict of Interest: The authors do not have any financial interest (equity holdings or stock options) in any corporate entity dealing with the material or the subject matter of this contribution. Neither did they have within the last 3 years, status as an officer, a member of the Board, nor a member of an Advisory Committee of any entity engaged in activity related to the subject matter of this contribution. There is no planned, pending, or awarded patent on this work by the involved institution. None of the authors received speaking fees at symposia on Hypericum.

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